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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,419	10/30/2003	Stacey Patterson	6704-30	7565

43463 7590 05/18/2007

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ART UNIT	**PAPER NUMBER**
1652	

MAIL DATE	DELIVERY MODE
05/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/697,419	PATTERSON ET AL.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7-12,14-27,29 and 31-33* is/are pending in the application.

4a) Of the above claim(s) *14-26 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4, 7-12, 14, 27, 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-2, 4, 7-12, 14-27, 29 and 31-33 are currently pending in the instant application.

Applicant's amendment of claims 1-2, 4, 9, 12, 14, 27, and canceling claims 3, 5-6, 13, 28 and 30 filed on 5/11/2005 is acknowledged. Claims 15-26 and 29 remain withdrawn as from further consideration pursuant to 37 CFR 1.142(b) as being drawn to an invention nonelected without traverse, there being no allowable generic or linking claim.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/26/2007 has been entered.

Thus, claims 1-2, 4, 7-12, 14, 27 and 31-33 are under consideration and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

Acknowledgement is made of applicants claim for priority of provisional application 60/422,467 filed on 10/30/2002.

New-Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-2, 7-12 and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite in the recitation of "codon optimized" which is confusing i.e. codon optimized for what? Codon optimization is a known process for expressing a gene encoding a protein in increased amount, which is specific for a particular species i.e. codon optimization for human is different from bacteria. It is not clear to the Examiner regarding above phrase whether the codon optimized for human or bacteria or for anything else? Accordingly, claims 2, 7-12 and 31-33 are rejected, as they are dependent on claim 1.

Claims 9-10, 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell transformed with the recited nucleic acids does not reasonably provide enablement for any cell within a multicellular animal which have been transformed with the recited nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 9-10, 12 and 14 are so broad as to encompass any cell transformed with specific nucleic acids, including cell in *in vitro* culture as well as cells within any multicellular organism. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of host cell broadly encompassed by the claims. While methods for transforming cell *in vitro* are well known in the art, methods for successfully transforming cells within complex multicellular organisms are not routine and are highly

unpredictable. Furthermore, methods for producing a successfully transformed cell within one multicellular organism are unlikely to be applicable to transformation of other types of multicellular organisms as multicellular organisms vary widely. However, in this case the disclosure is limited to only host cell in vitro.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the use of any cell within a multicellular organism for the production of polypeptide. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, expression of genes in a particular host cell having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is suggested that applicants limit the claims to "An isolated host cell".

Applicants argue that at the time the application was filed, methods of transforming cells within complex multicellular organisms were (and still are) routine and furthermore, applicants point to U.S patent no. 5,874,304 to Zolotukhin et al., wherein Example X in column 50 of said patent describes the expression of GFP in guinea pigs. Applicants also argue that a number of manuals and treatises teaching how to generate transgenic animals were known and available at the time the application was filed. See, e.g., Transgenic Animal Technology: A Laboratory Notebook, 1st ed., by Carl A. Pinkert. Elsevier Publishing, Cambridge, MA, 1994; and Transgenic Animals: Generation and Use, ed. Louis-Marie Houdebine, CRC Press, Boca Raton, FL, 1997, and one of skill in the art would predict that the cells described in the present

specification could be successfully incorporated into a multicellular animal. Because there was considerable direction and guidance in the specification as filed and a high level of skill in the art at the time the application was filed, the specification does enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims.

Applicant's arguments have been fully considered but are not persuasive for the following reasons:

Claims 9-10 and 14 still read on any cell or any mammalian cell, which encompasses multicellular human being that is non-statutory as well as non-enabled. While methods for transforming cell *in vitro* are well known in the art, methods for successfully transforming cells within complex multicellular animal are not routine and are highly unpredictable.

Furthermore, the prior art teaches that making genetically modified animals is highly unpredictable. The relevant art has for many years indicated that the unpredictability of generating transgenic animals lies with the site or sites of integration of the transgene into the target genome. Kappel et al. (Current Opinion in Biotechnology 3:548-553, 1992) teach that transgenic animals are known to have inherent cellular mechanisms, which may alter the pattern of gene expression, such as DNA methylation or deletion from the genome (page 549, right column, third paragraph). Furthermore, Mullins et al. (Hypertension 22(4): 630-633, 1993) teach that integration of a transgene in different species may result in widely different phenotypic responses (page 631, left column, first paragraph, last sentence). Also, Mullins et al. (J. Clin. Invest. 97(7): 1557-1560, 1996) teach that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being

addressed, bearing in mind that a given construct may react very differently from one species to another." (page 1559, Summary). Wigley et al. (Reprod. Fert. Dev. 6:585-588, 1994) indicate that transgenesis by microinjection has a number of limitations including random integration in the genome and integration of transgenes in multiple copies at one site such that expression level is not proportional to transgene copy number (page 585, Introduction). Cameron (Molecular Biotechnology 7:253-265, 1997) teaches that well-regulated expression of the transgene is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (page 256, left column, last three lines, right column, first three lines). According to Cameron, transgene expression with different transgenic lines produced with the same constructs is unpredictable and expression levels do not correlate with the number of transgene copies integrated, thus indicating the influence of the integration site on the expression pattern (page 256, right column, lines 3-13).

In regard to DNA delivery and expression in human tissues, the art teaches the high unpredictability of delivering DNA to human tissues and achieving the desired expression. For example, Phillips (J. Pharm. Pharmacology 53:1169-1174, 2001) teaches that the major challenges in gene therapy have been delivery of DNA to target cells and duration of expression (Abstract). According to Phillips, the problem regarding gene therapy is twofold in that (1) a system must be design to deliver DNA to a specific target while preventing degradation within the body, and (2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for a determined amount of time (page 1170, left column, lines 7-15). Gardlik et al. (Med. Sci. Monit. 11(4): RA110-121, 2005) teach that (1) while there are a number of methods known for delivery of DNA, there is no clear ideal delivery

system (RA119, last paragraph), and (2) the main problem in gene therapy lies in the secure and efficient delivery of genes into target cells and tissues (RA110, Summary).

Given the teachings of the art regarding the differences in expression of a transgene in different species, the limitations regarding the integration and expression of a transgene, the unpredictability of delivering and expressing DNA in human tissues, and in view of the lack of guidance provided by the specification, it would have required undue experimentation to engineer any transgenic multicellular organism, or cells thereof, as claimed. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 7-12, 27, and 31-33 are rejected under 35 U.S.C. 103(a) as being obvious over Szittner et al. (J Biol Chem. 1990 Sep 25; 265(27): 16581-7, see IDS), Mao et al. (Zhonghua Zhong Liu Za Zhi, 2001 Sep; 23(5): 359-62, article in Chinese) in view of Zolotukhin et al. (US Patent 5,874,304, publication 2/23/1999). Instant claims are directed to a codon optimized nucleic acid comprising a gene encoding LuxA protein from Photorhabdus luminescens, a vector comprising said gene having regulatory sequence, a transformed host cell and a kit comprising said nucleic acid molecule for analyzing gene expression.

Szittner et al. teach LuxA (luciferase) gene from Xenorhabdus (same as Photorhabdus) luminescens, which is 70% identical to SEQ ID NO: 1 of the instant application, wherein the source of LuxA gene also from Photorhabdus luminescens. Szittner et al. also teach the cloning of Lux genes required for expression of luminescence, complete nucleotide sequences of the LuxA gene coding for the alpha subunit of luciferase. Szittner et al. further teach that the luciferase from X. luminescens have a remarkably high thermal stability being stable at 45 degrees C (t 1/2 greater than 3 h) and suggested that the X. luminescens Lux system might be used for application in coupled luminescent assays and expression of Lux genes in eukaryotic systems at higher temperatures. Szittner et al. do not teach the use of codon-optimized or codon usage of LuxA gene for maximum expression with stability in eukaryotic or mammalian cells.

Mao et al. teach the expression of fused LuxAB gene of bacterial luciferase as a reporter gene in mammalian liver carcinoma cells. Mao et al. also teach cloning bacterial luciferase LuxA and B gene in the mammalian expression vector pcDNA3, wherein the promoter and enhancer is from cytomegalovirus (CMV) and transfected into BEL7402 cell and determined the luciferase

activity with standard assay method. Mao et al. do not teach codon-optimized LuxA gene.

Zolotukhin et al. teach a humanized green fluorescent protein (GFP) genes and method of use. Zolotukhin et al. also teach synthetic and humanized versions of GFP genes adapted for high-level expression in mammalian cells especially those of human origin by using base substitution in codons in order to change the codon usage for efficient expression in mammalian cells. Zolotukhin et al. also teach increase number of CTG or CTC leucine encoding codons, increase number of TTC for phenylalanine encoding codons and increase number of ATC isoleucine encoding codons of GFP amino acid sequence. Zolotukhin et al. also teach cloning the modified gene in expression vector and expressing in mammalian cells at higher efficiency.

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Szittner et al., Mao et al. and Zolotukhin et al. to codon-optimize luciferase gene of Szittner et al. including substituting the leucine codon CTG instead of other leucine codons as disclosed by Zolotukhin in order to optimum expression of said gene in mammalian cell and to clone the codon-optimized gene in mammalian expression vector under the regulation of promoter/enhancer as disclosed by Mao et al. to use the codon-optimized Lux system in the development a mammalian bioluminescence bioreporter system as a kit to be used in medical research and diagnostics applications.

One of ordinary skill in the art would have been motivated to use codon-optimized LuxA gene for mammalian cells in order to maximum expression of said gene in that mammalian cells for the efficient and stable enzyme activity in terms of luminescence to be used in medical research and diagnostics applications.

One of ordinary skill in the art would have a reasonable expectation of success because

use of codon-optimized gene for over-expression with higher stability in a mammalian cell is customary and widely used in the art.

Therefore, the above references render the claims 1-2, 7-12, 27, and 31-33 prima *facie* obvious to one of ordinary skill in the art.

Applicants argue that there is no motivation that is not persuasive because Zolotukhin et al. clearly show a motivation of using codon optimized nucleic acid molecule for optimum expression of luciferase gene in mammalian cells in order maximum expression of said gene in that mammalian cells for the efficient and stable enzyme activity in terms of luminescence to be used in medical research and diagnostics applications.

Claims 31-32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szittner et al. (J Biol Chem. 1990 Sep 25; 265(27): 16581-7, see IDS), Mao et al. (Zhonghua Zhong Liu Za Zhi, 2001 Sep; 23(5): 359-62, article in Chinese) in view of Zolotukhin et al. (US Patent 5,874,304, publication 2/23/1999) as applied to claims 1-3, 8-13, and 27 above, and further in view of Greer et al. (Luminescence. 2002 Jan-Feb; 17(1): 43-74, Review) and Lowe et al. (US Patent 6,132,983).

Szittner et al., Mao et al., and Zolotukhin et al. teach LuxA (luciferase) gene from Xenorhabdus, codon-optimized or codon usage of LuxA gene for maximum expression in mammalian cells as discussed above. Szittner et al., Mao et al., and Zolotukhin et al. do not teach the use of codon-optimized LuxA gene for making a kit for analyzing gene expression or using IRES promoter for expression.

Greer et al. teach LuxA gene from Photorhabdus luminescens and marine Vibrio harveyi bacteria, as well as eukaryotic luciferase luc and ruc genes from firefly species (Photinus) and the sea pansy (Renilla reniformis), respectively, that emit light in the presence of oxygen and a substrate (luciferin), cloning in a vector having selectable marker, expression using different promoter and enhancer including IRES in cell cultures, individual cells, whole organisms, and transgenic organisms. Greer et al. also teach humanized luciferase i.e. codon-optimized for expressing human cells. Greer et al. do not teach a kit for testing gene expression in cultured cells.

Lowe et al. disclose a luciferase gene encoding protein from Photinus species, cloning in expression vectors having restriction site, promoter and enhancer, host cells. Lowe further disclose a test kit and reagents for carrying out luminescence assay by using luciferase protein to determine the gene expression.

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Szittner et al., Zolotukhin et al. Greer et al and Lowe et al. to develop a test kit for carrying out luminescence assay to determine the gene expression as disclosed by Lowe et al. by using LuxA gene of Szittner et al. by optimizing the codon usage as taught by Zolotukhin et al. by using vectors having restriction sites, promoter/enhancer including IRES as well as selectable marker to determine a gene expression in a sample.

One of ordinary skill in the art would have been motivated to develop a testing kit using codon-optimized LuxA gene for determining gene expression in mammalian cell sample to be used in medical research and diagnostics applications.

One of ordinary skill in the art would have a reasonable expectation of success because making a testing kit by using codon-optimized luciferase to determine the gene expression is customary and widely used in the art.

Therefore, the above references render the claims 31-33 prima *facie* obvious to one of ordinary skill in the art.

Conclusion

Status of the claims:

Claims 1-2, 4, 7-12, 14-27, 29 and 31-33 are pending.

Claims 15-26 and 29 remain withdrawn.

Claims 1-2, 7-12, 27, and 31-33 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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